REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-18 and 20-40 are pending in this application, and claims 33-40 are withdrawn. Accordingly, claims 1-18 and 20-32 are currently presented for prosecution.

I. Claims 1-18 and 20-32 are Patentable Over WO 98/29134 and United States Patent No. 5,630,796

Claims 1-18 and 20-32 stand rejected as allegedly obvious over WO 98/29134 ("WO '134") in view of United States Patent No. 5,630,796 ("Bellhouse"). Claim 1 of the present application recites that particles are accelerated into and/or across an area of skin or mucosa using a needleless syringe device. Subsequently, a transdermal delivery device or an occlusive dressing is topically positioned over the area of skin or mucosa. The particles, transdermal delivery device, and/or the occlusive dressing may contain the therapeutic agent.

The Examiner argues that the claimed invention would have been obvious over WO '134 in view of Bellhouse. The Examiner's reasoning is that WO '134 teaches a method of enhancing the permeability of an active agent across a biological membrane, including skin and mucosa. The method of WO '134 includes carrying out microporation of the membrane at a site of administration, followed by contacting the porated surface with a permeant (for example, a therapeutic agent) and a permeation enhancer. The Examiner then argues that WO '134 suggests forming pores using "any" non-invasive technique that does not require entry of a needle or invasive instruments into the skin or mucosa.

The Examiner acknowledges, however, that the primary reference, WO '134, does not teach or suggest the use of a needleless syringe to carry out the microporation. Nevertheless, the Examiner argues that it would have been obvious to use the needleless syringe described in Bellhouse to carry out the microporation step described by WO '134, and then to apply a topical patch containing an active agent as described in WO '134. On that basis, the Examiner argues that the claims at issue are obvious over WO '134 in view of Bellhouse.

The Examiner asserts that one skilled in the art would have been motivated to combine these references because Bellhouse teaches that the needleless syringe method is a safe and quick method with less pain and no risk of infection. Finally, the Examiner asserts that a skilled artisan would have a reasonable expectation of successfully arriving at the claimed invention.

WO '134 describes a method for enhancing the permeability of a biological membrane to a permeant (for example, a therapeutic agent) using microporation. Microporation is carried out to form a micropore of selected depth in a biological membrane and the porated site is then contacted with the permeant. Additional enhancers may be applied to the site of administration to enhance both the flux of the permeant into the organism through the micropores as well as into targeted tissues within the organism. Several active agents can be used in the method described by WO '134, including polypeptides and vaccines, which are optionally associated with a carrier.

The types of microporation envisioned by WO '134 are described on page 16, lines 14 to 24. There, WO '134 describes five techniques that may be used to porate a biological membrane. Significantly, however, WO '134 does not mention the use of particles administered via a needleless syringe. While the passage does mention the use of a high pressure jet of fluid, it does so in the context of using the fluid itself to hydraulically puncture the biological membrane. This porating technique is, of course, very different from using a fluid to propel a particle across the biological membrane as would be the case with a needleless syringe. It is therefore clear that WO '134 does not disclose the use of a needleless syringe.

Once the selected area has been microporated, a therapeutic agent is applied to the surface as described at page 19, lines 6 to 14. Thus, WO '134 describes a method in which poration of a biological membrane occurs followed by the application of a therapeutic agent to that membrane.

Unlike WO '134, the claimed method is directed to an improved delivery technique using a needleless syringe. Since WO '134 is wholly silent as to the use of a needleless syringe, a skilled artisan would never have started with WO '134.

Bellhouse relates to a needleless syringe having a membrane that is ruptured by gas pressure to generate a supersonic gas flow in which particles containing a therapeutic agent are injected. However, Bellhouse teaches away from the suggested combination and instead suggests that it should not be combined with other documents. Bellhouse discloses a method that stands on its own as an effective transdermal delivery method of a therapeutic agent. For example, at column 1, lines 45 to 48 of Bellhouse, the specification states that the needleless syringe is "useful for routine delivery of drugs, such as insulin..., and could be of use in mass immunisation programs, or for the delivery of slow release drugs such as pain killers and contraceptives."

As such, Bellhouse makes clear that the needleless syringe described is useful for the routine delivery of drugs and is a *self-contained method* of drug delivery. Accordingly, it cannot reasonably be expected to be of use in a multi-step drug delivery technique where different drug delivery technologies are used to custom tailor drug delivery profiles as is claimed in the present application. The skilled artisan, therefore, is provided with no motivation to combine Bellhouse with WO '134 and, if anything, Bellhouse teaches away from the claimed invention.

The method disclosed in WO '134 is a separate and self-contained method of drug delivery. Absent some motivation to combine Bellhouse with WO '134, the Examiner cannot make out a *prima facie* case of obviousness. The Examiner, however, has not provided any reasoning why one skilled in the art at the time of the invention would have been motivated to combine a method for delivering a pharmaceutical agent with a needleless syringe as taught by Bellhouse with a second method for subsequently administering the pharmaceutical agent at the same mucosal site through a topical patch as taught by WO '134.

Neither reference suggests that such a multi-step drug delivery technique, where multiple different drug delivery technologies are used to custom tailor drug delivery profiles, would be desirable. Nor do they suggest that either method is incomplete or ineffective. Moreover, Bellhouse does not disclose using its device to administer strictly placebo particles, since the totality of Bellhouse relates to delivery of therapeutics. Finally, Bellhouse does not teach or suggest that its particles, even if administered in the order suggested by the Examiner, would result in enhanced delivery of a subsequently administered therapeutic as suggested by the Examiner.

Accordingly, one of ordinary skill in the art would not have been motivated to combine Bellhouse and WO '134 and the Examiner has not made out a *prima facie* case of obviousness. Instead, the Examiner rewrote the prior art, ignoring the clear teachings from the art, and arrived at an entirely inconsistent and unsupportable position. This is the hallmark of an improper hindsight reconstruction of applicants' claimed invention.

Finally, the Examiner's assertion that one skilled in the art would be motivated to combine the two references because Bellhouse teaches that the needleless method is a "safe [and] quick method with less pain and no risk of infection" is inapposite. Bellhouse does note that the "main advantages which flow from the invention include no needle and less pain, no risk of infection, delivery of drugs in natural solid form, quicker and safer to use than liquid drug, by syringe and needle and no sharps to dispose of." Bellhouse, col. 1, ll. 61-65.

However, nothing in either of the references suggests that the needless delivery method of Bellhouse would enhance the permeation of a subsequently administered therapeutic agent. Instead, Bellhouse clearly discloses that it is a method of delivering a therapeutic agent. The fact that the method is safe and quick, by itself, does not provide a motivation to combine the references. Accordingly, the Examiner's rationale does not provide any motivation to combine the Bellhouse method with a second method of delivering a therapeutic agent as disclosed in WO '134.

Finally, applicants wish to address the Examiner's assertion that WO '134 suggests forming pores using "any" non-invasive technique that does not require entry of a needle into the skin or mucosa. The Examiner cites page 32, lines 10 to 11, to support the proposition. Page 32, lines 10 to 11, defines the term "non-invasive" as "not requiring the entry of a needle, catheter, or other invasive instrument into the skin or mucous membrane." It does not, however, suggest that "any" non-invasive technique may be employed with the described method. In fact, WO '134 only discloses five methods of porating a biological membrane, none of which utilize the needleless injection technique taught by Bellhouse.

Moreover, although five types of poration are referred to in the description of WO '134, in reality, an even smaller number of specific types of poration is supported by the Examples of WO '134, namely the use of a laser, thermal ablation, sonic energy and a combination of sonic energy with a chemical enhancer. Yet again, this emphasizes the fact that there is simply nothing in WO '134 which suggests the needleless injection technique taught in Bellhouse.

II. Conclusion

One of ordinary skill in the art would not have been motivated to combine Bellhouse and WO '134 in the manner suggested by the Examiner to arrive at the claimed invention. Therefore, the Examiner has not made out a *prima facie* case of obviousness. As such, claim 1 is patentable over this combination of references. Since claims 2-18 and 20-32 are dependent from claim 1, for at least this reason, claims 2-18 and 20-32 are patentable over the prior art of record.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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